**This example** was created to help explain what CPHS committee members are looking for when they review this section of your proposal.

In this section, the Committee would like to know what you intend to learn from this study (" **Specific Aims"** ); what data you plan to collect ("**Primary Outcomes"**); what your expectations are about what this data might reveal (i.e. "**Hypotheses"**) and what sort of analytic plan you propose to attempt to corroborate your expectations.

*We are keenly focused on "connecting" the four components of Primary Outcome, Specific Aims, Hypotheses, and Statistics so that we can see that there you have developed a* ***clear path to knowledge****. The CPHS needs to understand this link because the knowledge you gain is what balances the risks that research participants are exposed to. Without a clear path to knowledge, no risk is worthy.*

To keep things simple, <u>we recommend that you select one or two PRIMARY outcomes</u> (dependant variables) that will be excellent representations of the effect that you wish to measure, describe, or compare. While you may collect other data to help augment your understanding, hypothesis driven research (including engineering research) is best described with only one or two outcomes that are most relevant.

Your <u>Specific Aims should focus on the main goal</u> ("specific") or goals that you hope to achieve. We recommend 1-3 Specific Aims. You are not limited to collecting ONLY the data necessary for your Specific Aims; most researchers/engineers collect additional secondary data to help augment their primary findings.

<u>Hypotheses statements should have a **clear link** to the Specific Aims</u>. Numbering both sections accordingly sometimes helps to establish the link. Each Aim should have at least one hypothesis, and hypotheses statements should be written with the statistical plan in mind, so that whatever data analysis you propose will easily answer your hypotheses.

Similarly<u>, your statistical planning should directly address each hypothesis</u>. Statistical analyses can be quite varied, from simple plots, to tabular descriptions of the data, or to applications of complex inferential methods. Do not feel obligated to "go overboard" on the statistical plan, but clearly present your plan for how the data will be used to address each hypothesis.

In the example here, try to appreciate the links among all four of these sections.

**Specific Aims (SA):**
<u>SA 1:</u> Characterize the changes in VO2max and other cardiovascular outcome measures during and after long-duration spaceflight.

<u>SA 2:</u> Assess the validity of using sub-max exercise with pre-specified workloads to estimate VO2max during spaceflight.

**Hypotheses:**
<u>Hypothesis 1 (per SA1):</u> Mean VO2max is reduced (relative to pre-flight) during the early phases of spaceflight.

Hypothesis 2 (per SA1): Mean VO2 max remains essentially unchanged during spaceflight after the initial reduction.

Hypothesis 3 (per SA1): VO2max is reduced from spaceflight levels immediately after landing, then gradually returns to normal pre-flight levels.

Hypothesis 4 (per SA2): Sub-max estimates of VO2max (using pre-specified workloads to estimate VO2max) during spaceflight will produce valid estimates of subjects' true VO2max .

**Primary Outcomes:**
Our primary dependant variables for all hypotheses include VO2, and heart rate. Covariates and other outcomes include workload, cardiac output, and stroke volume. All measures are observed pre-flight and multiple times during flight and post-flight.

**Statistics**
Hypotheses 1, 2 & 3 will be evaluated by use of a mixed-effects linear regression model with VO2max as the dependent variable. Predictor variables will include indicators for flight day (pre-flight = reference category), indicator informing the model of the whether the observations represent pre-flight (reference), during-flight, or post-landing/recovery, and indicators for recovery phases (0-3 days, 10-13 days, and 30+ days post-flight) will also be included.

- Hypothesis 1 will addressed by examining the sign and magnitude, with respect to its standard error, of the regression coefficient in the model that compares the earliest in-flight data to the pre-flight reference category. We anticipate a reduction in VO2 from pre-flight and will report the significance (p-level) and the magnitude of the mean difference with 95% confidence intervals.

- Hypothesis 2 will be evaluated by a-priori planned contrasts comparing the regression coefficients for the earliest in-flight data to subsequent in-flight data. We anticipate non-significant differences in VO2 among these flight days, but we will report the magnitude of the mean differences with 95% confidence intervals.

- Hypothesis 3 will be evaluated by a-priori planned contrasts comparing the sign and magnitude of the average of the in-flight coefficients to the immediate post-landing observation. We anticipate a reduction in VO2 from pre-flight and will report the significance (p-level) and the magnitude of the mean difference with 95% confidence intervals.

- Hypothesis 4 will be evaluated by comparing the observed (weight-adjusted) true VO2 max data with their sub-max estimates of VO2 max. Since we anticipate "similar" values, we will use an equivalency test statistic designed to test the null hypothesis that the difference (+/-) between weight-adjusted VO2Max and weight-adjusted estimated VO2max is less than or equal to TBD. Our report will describe the average observed differences with 95% confidence intervals, and the distribution of differences across the range of observed VO2Max scores, allowing us to determine whether or not observed differences are equally disturbed over the range of observations.